particles subsets. The aim of our work was to determine, by analyzing injected solutions, if the misuses of the generics could be more dangerous than that of the Subutex®.

Patients (or Materials) and Methods: Injection material used was contained in Steribox®II Kit. Solutions were prepared using Subutex® 8 mg or buprenorphine 8 mg generic as follows: tablet was dissolved in 1 mL of water, mashed with the syringe's piston, and filtered through a cotton pad or a Sterifilt®. Quantification of buprenorphine concentration was performed by U-HPLC; particles size distribution was performed by laser granulometry and flow cytometer.

Results: Seventy percent to 100% of the dose of buprenorphine contained in a tablet was found in the solution, whatever the drug and the filter used. After filtration with cotton pad, the maximal size of the particles found in solution reached 100 µm for the generic and 47 µm for Subutex®. With Sterifilt®, the maximal size of the particles were 36 µm for the generic and under the limits of the laser granulometer for Subutex®. These results were confirmed by flow cytometer: after Sterifilt® filtration, more particles >5 µm were found for the generic with regard to the princeps.

Conclusion: Extraction recovery of buprenorphine tablets was excellent and similar for both princeps and generic. These results confirm that buprenorphine remains an excellent candidate for misuse. We have highlighted the wide variation of the quantity and the size of the particles present in solution between the 2 drugs after cotton pad filtration. According to these preliminary results, misuse of injected buprenorphine could be more dangerous with the generic form than with the princeps, in particular in term of thromboembolic events.

Disclosure of Interest: None declared.

PP038—SOY DIET CAUSES HISTOLOGICAL CHANGES ON THE REPRODUCTIVE ORGANS OF ADULT MALE RATS

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Introduction: Soy products are used in human diet and in food additives because of their beneficial effects in menopause and their potential protective effects in cancer and other diseases. Nevertheless, genistein and other phytoestrogens contained in soy may disrupt the endocrine system by modulating the hypothalamic-pituitary-gonadal axis, and thus they may influence spermatogenesis and reproduction. The objective of this study was to investigate the adverse effects of chronic soy diet on the histologic characteristics of the reproductive organs in adult male rats.

Patients (or Materials) and Methods: Two groups of adult male albino Wistar rats, 6 months old, were used: the study group and the control group. The study group received ad libidum food enriched in soy protein for 3 months. The control group received ad libidum the standard food for 3 months. Both groups were grown under the same conditions and according to the rules of Good Laboratory Practice. The study was approved by the local ethics committee. The animals of both groups were sacrificed, and specimens of the reproductive organs were prepared and stained for microscopic examination. The preparations were observed by 2 different persons, blinded to the source of the specimen. Statistical analysis was performed with the statistical package SPSS.

Results: The seminiferous epithelium of the testes was found lower and contained fewer layers of spermatocytes in the study group compared with the control group. Similar changes were observed in the epididymidal epithelium and the epithelium of the vas deferens and the seminal vesicles of the study group. The number of spermatozoa in the seminiferous tubules of the testes, in epididymis, and in the vas deferens was much lower in rats fed with soy diet compared with the rats fed with standard food.

Conclusion: Chronic soy diet causes histologic changes in the reproductive organs and influences the number of spermatozoa in the testes of the adult rats. Diet containing phytoestrogens may influence male fertility and should probably be avoided in a chronic basis when pregnancy is desired.

Disclosure of Interest: None declared.

PP039—DIFFICULTIES IN PHARMACOVIGILANCE PRACTICES IN EUROPEAN NON-EU COUNTRIES AND THEIR DIFFERENCES FROM EU REQUIREMENTS

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Introduction: Enforcement of new EU Pharmacovigilance (PV) Regulation 1235/2010 and Directive 2010/84/EU, in July 2012, caused differencies from local PV regulations of some European non-EU countries. Consequently, disturbances of PV practices have been caused at local affiliates of international pharma companies who based their operational procedures on local law aligned with EU Legislation.

Patients (or Materials) and Methods: The review and comparison of EU PV Legislation and Local PV Regulation of Serbia 64/2011 were done. Main differences are listed and their impact on local PV practice is presented. Local PV regulation of Serbia was chosen becaue: (1) authors are from Serbia; and (2) the local regulation is more complex than others in the region.

Challenges in local PV practices are presented based on experience of Janssen local safety unit (LSU).

Results: Main differences: (1) Pharmacovigilance System Master File (PSMF) and Summary of Pharmacovigilance System (SPS) vs. Detailed Description of Pharmacovigilance System (DDPS);

(2)Periodicity and timelines for Periodic Safety Update Reports (PSUR) submission;

(3)European Risk Management Plan (EU RMP) vs. RMP

(4)Safety reports for renewals: Addendum Clinical Overview (ACO) vs. Summary Bridge Report (SBR) and Addendum report (AR).

(1)According to EU legislation, SPS has to be submitted to European Medicines Agency and PSMF only in case of explicit requirement. According to local requirements, global and local DDPS are needed. SPS is not enough. PSMF accepted, but could not be requested. Appropriate global document is milestone to be compliant and to obtain approval/renewal license.

(2)Locally, periodicity, and timeline for PSUR submission are still "old." However, Local Health Authority (LHA) accepts European Union Referens Dates (EURD) list for "centralized products" (CP) and for non-CP with renewals. Unevenness requires enhanced monitoring of PSUR periodicity and timelines and make compliance difficult.

(3)Locally, EU RMP is accepted. However, implementation is delayed since LHA based approval on EMA approval.

(4)Locally, SBR and AR are required for renewals. LHA tends to accept ACO, but currently, only as additional document. Consequences are additional effort and cost for Company to prepare SBR and AR, and ACO, in addition.

Overall, LHA has not had access to EudraVigilance database, and worldwide individual case safety reports have to be submitted to LHA by LSU, which is time-consuming.

Conclusion: LHA tends to accept EU requirements as much as it could match local regulation, but local regulation differs significantly from EU. As a consequence, LSU makes additional efforts and communications with LHA and Company, to fulfill each requirement in its own way. The differences could be overcome with harmonization of local regulation with EU and if LHA receive access to EudraVigilance database.
Disclosure of Interest: None declared.

PP040—DRUG INFORMATION UNIT–VALUABLE SOURCE OF INFORMATION, NOVI SAD EXPERIENCE

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Introduction: Medical and pharmaceutical professionals in Serbia gather information on drugs from the National Agency of Drugs and Medical Devices or from the various publications such as British National Fromulary and Physicians Drug Reference. General population can obtain information from their general practitioners (GP) or pharmacist. At Department of Pharmacology and Clinical Pharmacology, Medical faculty of Novi Sad, there exists a Drug Information Unit, regional center offering drug information to both professional and general population in Vojvodina (~1,600,000 inhabitants).
Patients (or Materials) and Methods: Clients require information by telephone (>99.5% request) or by e-mail. Interns in Clinical Pharmacology collect necessary data regarding the therapeutic problem (eg, age and sex of the patient, other drugs taken, present diseases). After case solving, and upon the approval from the senior clinical pharmacologist, interns deliver the information to the client (both by telephone and e-mail).
Results: About 3% of all requests are from general population (usually questions on interactions, side effects, dosing, and administration). Remaining requests are from health (20% from GPs and 80% from specialists) or pharmaceutical professionals. Almost 30% of all of the requests of the health professional are regarding possible drug–drug or drug–disease interactions. About 12% of requests are related to side effects of the administered drug. Pregnancy and lactation are subjects of interest in 15% of overall number of requests. Maximal doses allowed and posology have shares of ~11%. Remaining information is concerning the pharmacokinetics of the drug, first-line drugs for certain disease, dosing in children, etc.
Conclusion: According to our experience, the Drug Information Unit is quite useful source of information for both professionals and general population offering various information on different topics related to drugs.
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Disclosure of Interest: None declared.

PP042—SAFETY ASSESSMENT OF LOW DOSES OF METHADONE IN COMBINATION WITH BENZODIAZEPINES IN REAL OCCASIONS DURING METHADONE MAINTENANCE TREATMENT – A PILOT STUDY

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Introduction: Our study assessed the safety of low doses of methadone combined with benzodiazepines during first month of methadone maintenance treatment (MMT) in opioid addicts, according to differences in corrected QT (QTc) interval and side effects.
Patients (or Materials) and Methods: The study included patients with a diagnosis of opioid dependence, who were referred to the MMT at the Clinic of Psychiatry, Clinical Centre of Vojvodina, Novi Sad, during 2012. All patients were interviewed about their age, duration of heroin misuse, and the presence of ECG disorders in the first-degree relatives. One month after the beginning of MMT, they were interviewed about experienced side effects. Data about applied methadone dose and the use of benzodiazepines were collected from the medical history of each patient. Before the methadone intake for the first time and 1 month after the beginning of MMT, all patients underwent a 12-lead ECG. The QTc was calculated using Bazett's formula.
Results: A total of 20 patients were enrolled in the study during the observed period. Their average age (SD) was 32.21 (5.63) years. The average heroin misuse time (SD) was 11.95 (4.02) years. In the patients' history, no cardiovascular diseases were reported, as well as sudden cardiac death or family history of long QTc in the first-degree relatives. A statistically significant increase ($P < 0.05$) in the length of QTc intervals measured after 1 month of MMT (QTc1) in comparison with those at the baseline (QTc0) was observed. The mean (SD) methadone dose was 45.26 (15.41) mg. The most frequently used drug in combination with methadone was diazepam, which was used in 85% of patients. The mean dose (SD) of diazepam was 30.93 (10.36) mg. A statistically significant dose-dependent correlation between concomitantly used diazepam daily dose and QTc1 ($R2 = 0.47$, $P = 0.008$) was revealed, but without a statistically significant dose-dependent correlation between methadone and QTc1 ($P = 0.960$). The most commonly reported side effects were sweating (65%), obstipation (60%), and itch (55%). None of participants experienced any cardiac side effects.
Conclusion: With respect to the results, it would be advisable to perform both pretreatment and regular ECG checkup after 1 month of MMT, especially in case of concomitant use of benzodiazepines.
Key words: methadonebenzodiazepinesQTc intervalinteractions-safety
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PP043—THE INFLUENCE OF HE EDUCATIONAL AND ADMINISTRATIVE MEASURES ON THE TREND OF USE OF UTEROTONICS

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Introduction: According to the recommendations of the World Health Organization, ergot alkaloids are neither the drug of first choice for the induction of the labor and not for the treatment of the postpartum hemorrhage because of their harmful side effects. The objective of this research was to follow the influence of the educa-